xenogeneic DNA segment of at least 100 kb which method comprises:

combining under fusing conditions said available embryonic stem cells and yeast spheroplasts, said spheroplasts containing a yeast artificial chromosome (YAC) comprising said xenogeneic DNA segment and including a marker for selection, whereby said xenogeneic DNA segment becomes stably integrated into the genome of said embryonic stem cells; and

selecting for an embryonic stem cell carrying said xenogeneic DNA segment by means of the marker.

2. (Amended) An improved method for producing a modified nonhuman animal, said animal having a nonyeast xenogeneic DNA segment of at least 100 kb stably integrated into the genome of at least some of the germ cells of said animal, said method comprising:

combining under fusing conditions embryonic stem (ES) cells of an available ES cell line derived from said animal and yeast spheroplasts, said spheroplasts containing a yeast artificial chromosome (YAC) comprising said xenogeneic DNA segment and including a marker for selection, whereby said xenogeneic DNA segment becomes integrated into the genome of said embryonic stem cells;

selecting for embryonic stem cells carrying said xenogeneic DNA segment by means of the marker; and

transferring said embryonic cells into a host blastocyst, implanting said blastocyst in a pseudopregnant animal recipient, and allowing said blastocyst to develop to term to produce a chimeric animal carrying said xenogeneic DNA segment integrated into the genome of at least some of the germ cells of said animal.

3. (Amended) An improved method for producing a modified nonhuman animal, said animal having a nonyeast xenogeneic DNA segment of at least 100 kb stably integrated into the genome of all cells of said animal, said method comprising:

combining under fusing conditions embryonic stem cells of an available ES cell line derived from said animal and yeast spheroplasts, said spheroplasts containing a yeast artificial chromosome (YAC) comprising said xenogeneic DNA segment and including a marker for selection, whereby said xenogeneic DNA segment becomes integrated into the genome of said embryonic stem cells;

selecting for embryonic stem cells carrying said xenogeneic DNA segment by means of the marker;

transferring said embryonic cells into a host blastocyst and implanting said blastocyst in a pseudopregnant animal recipient, and allowing said blastocyst to develop to term to produce a chimeric animal carrying said xenogeneic DNA segment in the genome of at least some of the germ cells of said animal; and

mating said chimeric animal with an animal of the same species to produce said modified animal carrying said xenogeneic DNA segment in all cells of said animal.

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5. (Amended) A method according to any of claims 1, 2 or 3, wherein said xenogeneic DNA is human DNA[, and/or wherein said xenogeneic DNA is immunoglobulin DNA in substantially intact form].

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6. (Amended) Embryonic stem cells comprising a genome modified according to the method of claims 1, 4, [or] 5 or 12.